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ORIGINAL ARTICLE

The efficacy of Jujube syrup on the prevention of drug-induced hepatotoxicity in pulmonary tuberculosis patients: A pilot randomized double-blind placebo-controlled clinical trial

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Abstract

Liver injury is the most common complication of anti-tuberculosis drugs that can cause significant problems. The study aimed to determine the effectiveness of *Jujube* syrup on the prevention of antituberculosis drug-induced hepatotoxicity (DIH). This pilot randomized double-blind study was conducted based on a placebo-controlled design in patients with tuberculosis (TB). The patients were divided into two groups based on the block random allocation method and received 10 cc of *jujube* or placebo syrup per day. The liver enzyme levels were assessed as primary outcomes, and the severity of cough, anorexia, and nausea along with the quality of life (QOL) was assessed as secondary outcomes. Finally, eight and nine patients in the *jujube* and placebo groups completed the study, respectively. In the second week of the study, 27.3% of the patients in the placebo group developed hepatotoxicity. Moreover, there was no liver toxicity in the *jujube* group. This difference between the two groups was statistically significant ($p = .037$). Furthermore, the severity of cough in patients in the jujube group decreased significantly during weeks 2 and 4. The QOL significantly improved in the *jujube* group, compared to the placebo group. This study suggested that *Jujube* syrup could prevent anti-TB DIH. It can also improve the severity of cough and the QOL in pulmonary TB patients.

KEYWORDS
antioxidant, drug-induced hepatotoxicity, Jujube, traditional Persian medicine, tuberculosis

Abbreviations: DIH, drug-induced hepatotoxicity; dl, deciliter; DOTS, Directly Observed Therapy Short-Course; mg, milligram; ml, milliliter; ng, nanogram; QOL, quality of life; SF36, short form health survey questionnaire; SPSS, Statistical Package for Social Sciences; TB, tuberculosis; VAS, visual analog scales; WHO, World Health Organization; µg, microgram.

Trial Registration: This study was registered in the Iranian Clinical Trials Registration Center (registration code IRCT20181107041586N1) on 2019-08-10.

1 | INTRODUCTION

Tuberculosis (TB) is one of the 10 leading causes of death among infectious agents. A total of 1.4 million people died due to TB in 2019.[1] Although the first-line treatment regimen of TB has been significantly successful, these medicines have significant side effects. Hepatotoxicity is the most serious and dangerous of anti-TB drug-induced complications with an incidence rate between 2% and 28% reported in various studies.[2,3] The liver injury caused by anti-tuberculosis-drugs leads to increased morbidity and mortality, treatment withdrawal, drug interruption, dose reduction, and selection of drug-resistant organisms.[4] No standard protocol has been proposed to address this important complication, therefore, any preventative measures that can reduce the incidence of hepatotoxicity and its complications will be clinically significant. Previous studies have shown that some compounds, such as N-acetyl cysteine,[5] silymarin,[6] and ginger,[7] can play a preventive role against hepatotoxicity.

Another important plant in this regard is *Ziziphus Jujuba* from the Rhamnaceae family. *Jujube* fruit, which has a relatively sweet taste and significant mucilage, has been available in the food basket of different societies in the world for many years (In Persian, the dried drupes are known as Annab).[8] This herb is one of the medicines widely prescribed in traditional Persian medicine for the prevention and treatment of liver diseases. It has also been used for treatment of chronic cough, anorexia, and digestive problems (which are common complications of TB),[9] Nonetheless, some side effects have been reported for this herb according to some recently conducted studies.[10]

The main biologically active components of *jujube* include vitamin C, phenolic, flavonoids, triterpenic acid, and polysaccharides.[11,12] Phenols are one of the most important compounds in jujube fruit, moreover, they particularly have a significant effect on resistance to oxidative stress. In general, these compounds have a significant level of antioxidant activity and free radical scavenging, which seems to be one of the main reasons for the role of *jujube* in hepatoprotection.[13,14] In addition to its antioxidant properties, its immune-stimulating, antimicrobial, anti-inflammatory, hepatoprotective, and gastrointestinal properties have been reported in various studies.[11]

However, in animal models, *jujube* has been effective in preventing drug-induced hepatotoxicity (DIH).[13,15,16] To the best of our knowledge, there has been no trial investigating the effect of this herb on the anti-TB DIH in humans. It is worth mentioning that no significant side effects, toxicity, and drug interactions of *jujube* have been reported in the studies.[17] Considering the importance of preventing and controlling liver complications induced by anti-TB drugs, as well as gastrointestinal and pulmonary benefits of *jujube*, this placebo-controlled double-blind randomized study aimed to investigate the effectiveness of jujube syrup on preventing hepatotoxicity induced by anti-TB drugs. Moreover, it was attempted to evaluate the effects of this syrup on digestive problems, cough, and quality of life (QOL) of these patients.

2 | MATERIALS AND METHODS

2.1 | Overview

This multicenter study was performed in Urban Health Centers and Rural Health Houses in five cities of Golestan province, Iran, under the supervision of Golestan Health Deputy affiliated to Golestan University of Medical Sciences, Gorgan, Iran. The study protocol was approved by the Research Committee and Medical Ethics Committee of Mazandaran University of Medical Sciences (ethic code: IR.MAZUMS.REC.1398.220) and registered in the Iranian Registry of Clinical Trials (ID: IRCT20181107041586N1). All relevant paragraphs of the Helsinki Declaration were considered in this study,[18] and written consent was obtained from all patients. This pilot, double-blind, randomized, superiority, and exploratory controlled trial was performed to evaluate the effectiveness of Jujuba syrup on the prevention of hepatotoxicity induced by anti-TB drugs from November 6, 2019 to June 4, 2020. This article is written according to the "CONSORT extension for Pilot and Feasibility Trials Checklist" that is attached.

2.2 | Material preparation

Jujube fruit with the scientific name of *Ziziphus Jujuba Mill* (syn: *Ziziphus Vulgaris Lamarck*) from the Rhamnaceae family was obtained from Birjand, Iran, in May 2019 and identified and approved by Mohammad Kamalinejad with herbarium number of SBMU-8108 in the Faculty of Pharmacy of Shahid Beheshti University of Medical Sciences, Tehran, Iran. It should be noted that after washing and drying, this fruit was ready to prepare the medicine.

2.3 | Standardization of the Ziziphus Jujuba extract

2.3.1 | Measurement of total phenolic compounds

The total amount of phenolic compounds was measured using the Folin-Ciocalteu method (as a reagent), and Gallic acid was used as the standard phenolic compound for measurements. The results were then expressed in milligram of Gallic acid per gram of extract. Folin-Ciocalteu is one of the most common methods for measuring phenolic compounds. The basis of this method is the reduction of Folin reagent by phenolic compounds in an alkaline environment and the formation of a blue complex that shows the maximum absorption at a wavelength of 765 nm.[19] For this purpose, one ml of Gallic acid solution in different dilutions (20, 40, 60, 80, and 100 μg/ml) was mixed with 5 ml of diluted Folin-Ciocalteu reagent in a ratio of 1:10 and incubated at room temperature. After 10 min, 4 ml of 7.5 mg/ml sodium carbonate solution was added, and the final mixture was incubated at room temperature for 30 min away from light. After this period, the uptake of each sample of Gallic acid was measured at 765 wavelengths.

This experiment was repeated three times for each of the gallic acid dilutions. Following that, based on the obtained absorption information, the gallic acid calibration curve was drawn as a linear absorption curve against concentration. The same method was used for the sample; however, instead of 1 ml of gallic acid, 1 ml of aqueous extract of 1.25 mg/ml was used, and the total phenolic content was calculated using the standard curve of Gallic acid. As a result, due to the reaction of the extract with the Folin Cicalto reagent and based on its comparison with standard gallic acid solutions and according to the linear equation obtained from the standard gallic acid curve, 7.7 μg/dl was obtained in 5 cc of syrup.

2.3.2 | Measurement of total flavonoid compounds

In this study, the spectrophotometer method was used along with an aluminum chloride solution as a reagent and routine, as well as a standard flavonoid compound for assays. Calorimetric technique was used for flavonoids estimation. The method of aluminum chloride colorimetric is that aluminum chloride forms acid stable complexes with the C-4 keto group and the C-3 or C-5 hydroxyl group of flavones and flavonols, which have the highest absorption at 415 nm.[20]

For this purpose, 2.5 ml of routine solution in different dilutions (20, 40, 60, 80, and 100 μg/ml) with 2.5 ml of an ethanol solution of aluminum chloride (20 mg/ml) was incubated at room temperature. After 40 min, the absorbance of each sample was measured at 415 nm. This experiment was repeated three times for each of the routine dilutions, and a routine calibration curve (absorption line curve against concentration) was drawn based on the obtained absorption information. The same method was performed for *jujube* aqueous extract; however, routine extracts with concentrations of 1.25 and 2.5 mg/ml were used in this study. The test was negative and the concentration of flavonoids was zero.

2.4 | Syrup preparation

Initially, 100 g of dried *jujube* fruit without seeds (pulp) were added to 500 cc of distilled water and boiled on a lamp flame in the laboratory for 10 min. After cooling, the content of the container was mixed thoroughly, and it was then strained using a suitable filter. In the next stage, the water in the extract was evaporated using a Bain-marie to obtain a dry extract. Therefore, 15 g of dry extract was obtained from 100 g of dried *jujube*. As a result, 10% of *jujube* syrup was obtained using the USP34 simple syrup formula with 66.7% sugar concentration.

The placebo was prepared based on the USP simple syrup formula with a sugar concentration of 66.7%. The microbial and physicochemical controls and necessary standardizations were performed, and the phenolic and flavonoid compounds of total syrup were determined at the Faculty of Pharmacy of Shahid Beheshti University, Tehran, Iran. Both types of syrup were prepared in amber glass bottle with appropriate labels.

2.5 | Patients

The statistical population included all new cases of pulmonary TB, living in Gorgan, Aliabad, Azadshahr, Ramian, and Gonbad in Golestan province, Iran. The patients were selected from urban and rural health centers affiliated to the Golestan University of Medical Sciences. Patients who met the following criteria were enrolled to the study: those were willing to participate with the study and gave written consent forms, age range of 18–68 years, diagnosed with pulmonary tuberculosis by an infectious disease specialist or a physician and planned to receive a standard antituberculosis treatment regime.

The participants were excluded if they met the following criteria: active liver and kidney diseases, pregnant or lactating women, patients with elevated serum alanine aminotransferase enzyme (ALT) and aspartate aminotransferase (AST) (more than 3 times of upper normal limit), the occurrence of any severe drug side effects in the course of the study, and consumption of less than half of the medicine for any reason.

2.6 | Sample size

Based on the values obtained from a pilot study at the level of $\alpha = .05$ and $\beta = .20$, the sample size was determined at 24 cases in each group based on the average comparison formula.

2.7 | Randomization, allocation concealment, and blinding

The random allocation of participants based on computerized- system with a block of two and four was performed by a statistician who was not involved in recruitment of patients. The randomization list was then sealed in an opaque envelope. A research assistant opened envelops and treatments were assigned to patients who met the inclusion criteria, accordingly. All of medicines were obtained from the Faculty of Pharmacy, numbered, and coded with a label and only a statistician knew about the details of the study drugs that the patients received. As a result, the outcome assessors were blind. The eligible participants were randomly allocated to the *jujube* syrup or placebo group in a 1:1 ratio. *Jujube* syrups and placebo were similar in appearance (in glass bottle of the same shape and size) and drug concentration. In addition, the remaining were hidden from the study executors and participants until the end of data analysis (double-blind).

2.8 | Study intervention

The patients with newly pulmonary TB were registered after diagnosis in the TB register system. The first-line anti-TB drugs, including Isoniazid (5 mg/kg/day), rifampin (10 mg/kg/day), ethambutol

(15 mg/kg/day), and pyrazinamide (25 mg/kg/day), were administered once a day at fasting time. The *jujube* syrup group was given a dose of 10 cc per day (5 cc twice daily), 20 min after breakfast and 20 min after dinner. The patients were assigned to 2 groups as soon as the diagnosis of TB was confirmed by a TB physician and were routinely treated with anti-TB by DOTs according to the national TB guideline and in dosage calculated according to the patient's body weight.

The amount of syrup consumed was evaluated weekly on the days of follow-up to check the patient's compliance and adherence. Furthermore, the side effects were recorded daily by DOTs executives. After the initiation of the study, as well as at the end of weeks two and four, the patients were referred for clinical evaluation and sampling of liver enzymes; then they were visited by the researcher.

In addition to the daily care, participants were evaluated by telephone every week for the incidence and severity of drug side effects or any other complications. Although the required information was explained orally, all necessary advice about the amount of consumption, duration of treatment, and how to use the medicine were provided to patients in written notes. In order to match and create similar behaviors in all participants in this study, the protocol of how to take the drug was reviewed occasionally. Moreover, the patients were given the necessary training and they were asked to contact the researcher by telephone if they had any questions or problems during the treatment period.

2.9 | Study outcomes

Blood samples were drawn to evaluate liver enzymes as the primary outcome at the beginning of the study, as well as the end of weeks 2 and 4. In total, 2 cc of blood samples were transported to the laboratories, and then after serum separation with cold chain were sent to Gorgan Health Center laboratory as soon as possible, so that all samples were measured in a common laboratory and with the same kits using a BS-480 (Mindray) auto-analyzer (manufactured by Pars Azmun, Iran). The Visual Analogue Scale (VAS) was completed on day 0 and at the end of weeks 2 and 4 for evaluating cough, anorexia, and nausea, with scores of 0 and 10 indicating "no sign" and "severe signs," respectively. The validity of the VAS was assessed by an expert pharmacist. Moreover, the standard QOL form (SF36) with confirmed validity and reliability in Iran was completed by the researcher on day 0 and at the end of week four.[21]

Hepatotoxicity was defined as follows: 1- elevated serum ALT or AST more than 3 times of upper normal range with one of the symptoms of nausea and vomiting, anorexia, weakness, pain in the right upper quadrant of the abdomen and jaundice; or 2- elevated serum ALT or AST more than 5 times of upper normal range without clinical symptoms. In either case, the patient was referred to an infectious disease specialist. If the doctor stopped taking anti-TB drugs, the syrups would be stopped. The *jujube* syrup or placebo would be started again simultaneously with the re-use of anti-tuberculosis drugs.

2.10 | Statistical analysis

The data were analyzed in SPSS software (version 18) and R software. Subsequently, the quantitative and qualitative variables were described by mean ± SD, as well as frequency distribution tables and graphs, respectively. Moreover, the normality of quantitative trait distribution and the homogeneity of the variance-covariance matrix were assessed using the Shapiro-Wilk test and the Mauchly's Test of Sphericity, respectively. Repeated analysis of variance was also used to evaluate the effect of medicine, time, and drug-time interaction. Due to the random assignment of individuals into two groups, repeated measures analysis of covariance was utilized to adjust the effect of intervening variables. A p-value of less than .05 was considered statistically significant.

3 | RESULTS

In total, 82 patients were evaluated regarding the eligibility criteria, and 48 cases were excluded from the study due to the lack of complete admission requirements ($n = 41$) and decline to participate in the study ($n = 7$). Thirty-four patients were enrolled to the study. In the first follow-up, which was performed during the first two weeks of the study, 12 patients were excluded from the study. In the *jujube* group, six cases were excluded from the study due to COVID-19 ($n = 4$), migration ($n = 1$), and medication discontinuation (due to side effects) ($n = 1$). Similarly, six cases in the placebo group were excluded from the study due to COVID-19 ($n = 3$), migration ($n = 2$), and unwillingness to continue the study ($n = 1$). Out of 11 patients who were analyzed at the end of the second week in two groups, three cases in the *jujube* group (death [$n = 1$], COVID-19 [$n = 1$], and migration [$n = 1$]) and two patients in the placebo group (death [$n = 1$] and TB misdiagnosis [$n = 1$]) failed to continue the study. Finally, 8 and 9 participants in the *jujube* and placebo groups completed all stages of the trial and were analyzed statistically, respectively (Figure 1: flow diagram).

Demographic and clinical characteristics of the patients in the *jujube* and placebo groups are shown in Table 1. The mean age and BMI of the patients were 64.17 ± 7.17 years and 27.28 ± 4.08 kg/m^2, respectively. It is worth mentioning that the majority of the participants were female (85.7%). No significant difference was observed between the groups regarding demographic characteristics and baseline clinical as well as para-clinical data. It is noteworthy to mention that diabetes mellitus was the most frequent underlying chronic diseases in the participants (22.7%).

In total, 3 (27.3%) and 0 (0%) patients in the placebo and jujube groups experienced anti-TB DIH. The difference between jujube and placebo groups regarding the incidence of DIH was statistically significant with Likelihood Ratio test ($p = .037$). Moreover, all patients were hepatotoxic during the first two weeks of treatment, and no patients developed hepatotoxicity during weeks three and four. In the cases with anti-TB-induced hepatotoxicity, anti-TB drugs were ceased temporarily, and after returning the liver enzymes to normal values and

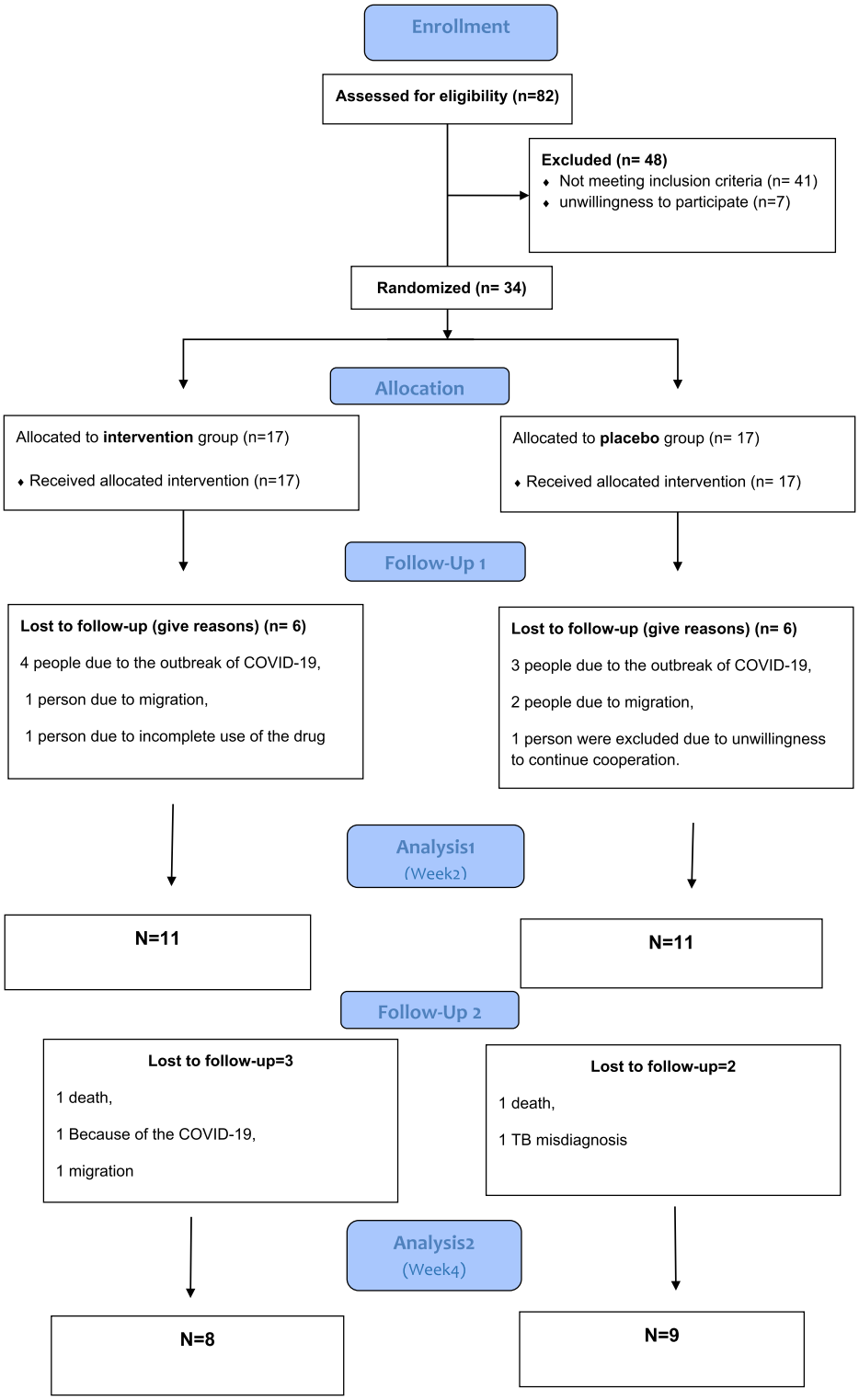

FIGURE 1 CONSORT 2010 flow diagram

resolution of disease-related symptoms, anti-TB medications were reintroduced gradually in a stepwise manner. Hepatotoxicity did not reoccur in any patient, and no further interventions were applied for the management of anti-TB-induced hepatotoxicity.

The levels of liver enzymes at weeks two and four in the *jujube* and placebo groups are shown in Table 2, respectively. Moreover, time trends in percent changes of AST and ALT enzymes are shown in Figures 2 and 3. In both cases, the mean changes of enzyme levels were almost the same. During the first two weeks of treatment, the mean enzyme levels increased in the placebo group. No increase was observed in the *jujube* group in terms of the enzyme levels. There was a significant difference between the two groups regarding the

TABLE 1 The patients' demographic characteristics

Characteristic	Total patients	Jujube group	Placebo group	*p*-value
Sex (Female) (%)	50.0	54.5	45.5	NS
Diabetes mellitus (%)	22.7	18.2	27.3	NS
Smoking (%)	31.8	27.3	36.4	NS
Addiction (%)	40.9	36.4	45.5	NS
Smear sputum (+) (%)	72.7	72.7	72.7	NS
Cough (%)	66.7	66.7	66.7	NS
Hemoptysis (%)	22.7	18.2	27.3	NS
Weight loss (%)	77.3	81.8	72.7	NS
Sweating (%)	77.3	81.8	72.7	NS
BMI (Mean)	20.9	21.3	20.6	NS
AST baseline (Mean)		24.1	22	.59
ALT baseline (Mean)		24.1	18.7	.34
ALP baseline (Mean)		310.5	247.8	.60

Abbreviation: NS, no significant.

levels of AST enzyme considering the baseline values of the enzyme as covariates ($p = .039$); nonetheless, it was not significant in terms of ALT ($p = .114$). The trend of AST and ALT changes is shown in Figures 2 and 3. According to the values of liver enzymes, the Cohen effect sizes were obtained at 0.841 and 0.592 for AST and ALT, respectively. According to Cohen, the former is classified as a large effect size, and the latter is regarded as the medium effect size.

Cough severity was evaluated as a secondary outcome with VAS during weeks two and four of the study. The trend of changes in mean cough is shown in Figure 4. The mean severity of coughs in the week two (0.046) and four (0.024) was reduced significantly in the *jujube* group. Gastrointestinal symptoms, including nausea and anorexia, were also evaluated as other secondary outcomes by the VAS scale; however, no significant difference was observed between the two groups in this regard. The QOL measured by the SF36 questionnaire at the end of the first month was improved in the *jujube* group compared to the placebo, which was statistically significant ($p = .032$). This level of significance was observed in the physical dimension ($p = .01$); however, the psychological dimension was close to the significance level ($p = .096$). The comparison of the mean of the secondary outcomes between the 2 groups is given in Table 3.

TABLE 2 Comparison of liver enzyme levels between the two groups

Liver enzyme (mean)	Jujube group	Placebo group	*p*-value
AST			
Baseline	24.118	22.000	.591*
Weak 2	20.330	44.273	.039**
Weak 4	23.500	24.556	.757**
ALT			
Baseline	24.21	18.72	.344*
Weak 2	21.66	44.00	.114**
Weak 4	21.75	31.55	.234**
ALP			
Baseline	310.54	247.82	.266*
Weak 2	291.70	224.45	.60**
Weak 4	207.25	226.33	.12**

*t - student test.; **ANCOVA test by Enzyme before Covariate.

3.1 | Adverse drug reactions

During the study, no significant adverse reactions were found regarding the consumption of the *jujube* syrup. In addition, no patients ceased *jujube* treatment because of its adverse reactions. Furthermore, serious adverse effects related to anti-TB drugs were not noted in this study. Additionally, no case of acute hepatic failure or fulminant hepatitis was detected in this study. There were no significant differences between the two groups regarding the incidence of mild adverse effects (nausea, itching, anorexia, and heartburn).

4 | DISCUSSION

The DIH is an important complication of anti-TB drugs that can occur during the first two months of treatment, especially when isoniazid, rifampin, and ethambutol are used concomitantly. The incidence rate of this complication can be as high as 27.7 percent. Some medications may be able to prevent the hepatotoxicity of TB drugs. *Jujube* played an important role in the prevention and treatment of liver problems in Persian Traditional medicine. In recent years, studies have been conducted on the preventive effects of *jujube* on DIH in the animal phase. This double-blind randomized clinical trial was conducted to evaluate the effectiveness of *jujube* on the prevention of hepatotoxicity of anti-TB drugs for the first time in human samples.

The effectiveness of *jujube* was determined by comparing ALT and AST levels, as well as the incidence of hepatic toxicity in the *jujube* and placebo groups. Endpoint analysis was performed at the end of week 4, since most enzymatic changes occurred in the first month of treatment during the studies.[22] The results of study conducted by Baghaei and Tabarsi reported that the highest probability of hepatotoxicity occurred during the first two weeks, as observed in this study.[22,23]

In the present study, none of the patients were hepatotoxic at the end of the first month, and the mean enzyme levels in the placebo group increased as expected due to anti-TB drugs during the first two weeks of treatment. Moreover, no increase was observed in the enzyme levels in the *jujube* group. However, it was found that this difference between the two groups was significant regarding the levels of AST enzyme, and it was not significant in terms of ALT. In line with these results, the study of Luangchosiri et al., which aimed to "determine the effect of silymarin for the prevention of anti-TB drug-induced liver injury", revealed that the maximum ALT level during 4 weeks after initiation of anti-TB treatments was

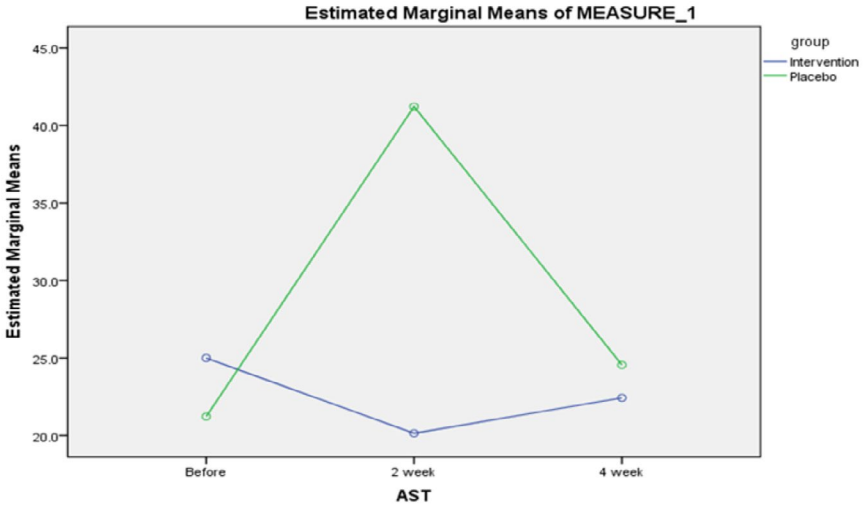

FIGURE 2 The trend of change in AST during study

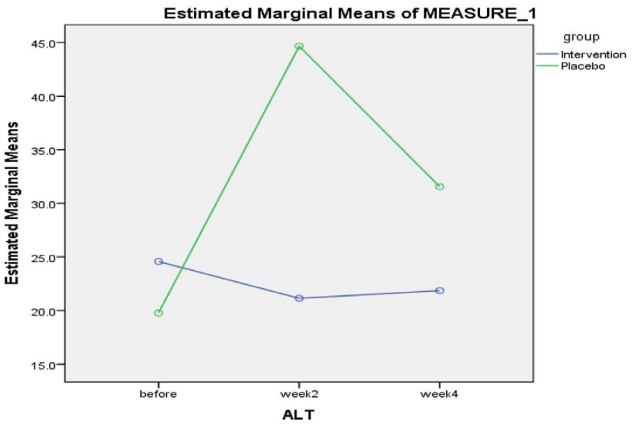

FIGURE 3 The trend of change in ALT during study

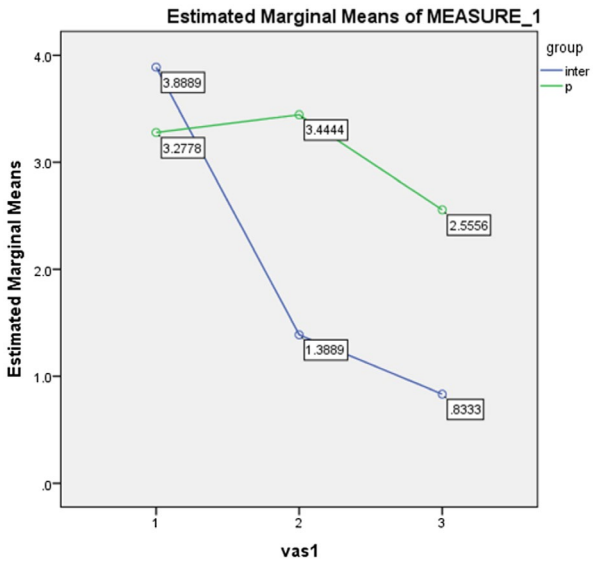

FIGURE 4 The trend of change in cough severity during study

not different between the groups. They suggested that the risk of antiTB-DILI was significantly higher in the placebo than in the silymarin group.[6]

Many studies suggested that anti-TB drugs cause hepatotoxicity or liver injury mainly due to excess free radical formation. Antioxidants are compounds that inhibit the activity of free radicals and prevent their oxidative attacks. Additionally, they protect the body's cells from the destructive effects of these compounds by inactivating them. The mechanism of these antioxidants includes the prevention of the extension of oxidation chain reactions by hydrogen atoms transfer to the formed free radicals. Among antioxidants, phenolic compounds are the most effective because they are good hydrogen donors.[24]

According to studies, the antioxidant activity of different parts of herbs depends on the total amount of their phenolic compounds.[25] Considering that the total phenol content of the *jujube* syrup was 7.7 micrograms per deciliter in 5 cc of syrup, the hepatoprotective effects of *jujube* can be attributed to its phenolic compounds. Phenols are formed in response to environmental stresses in plants, and due to their hydroxyl groups, they can act as electrons or hydrogen donors and neutralize free radicals.[24]

In this study, the mean severity of coughs in weeks 2 and 4 was statistically and significantly reduced in the *jujube* group compared to the placebo group. New studies have also confirmed the antitussive effects of *jujube* in children and also in dry cough.[26,27] The Ziziphus *jujube* contains abundant tannins, which have an effect on the pharyngeal-laryngeal mucosa and modulate them to decrease exudation, it provides a protection against the contact of any antigen (pathogen/allergen), and tannins also have local antimicrobial action which annihilates the microbes coming in contact. Thereby, tannins can justify the antitussive effects of *jujube*.[27]

Although the improvement in constipation was not a consequence of the current study, 18% of the patients explicitly reported an improvement in defecation status in the *jujube* group, which appears to be due to the abundant mucilage in the *jujube*. According to the results of several studies, it is recommended to focus more on this issue in future studies.[28]

In general, QOL is expected to increase in patients after treatment initiation and progression of the recovery process.

TABLE 3 Comparison of mean secondary outcomes between the two groups

Outcome	Jujube group	Placebo group	*p*-value
Cough			
Baseline	3.889	3.278	.510
Weak 2	1.389	3.444	.046
Weak 4	0.833	2.556	.024
Anorexia			
Baseline	3.882	4.056	.851
Weak 2	1.444	1.444	.719
Weak 4	0.667	1.444	.327
Nausea			
Baseline	1.667	2.444	.792
Weak 2	0.389	0.778	.496
Weak 4	0.222	0.667	.332
Quality of life			
Baseline	26.19	29.50	.437
Weak 4	76.82	62.26	.032

Accordingly, an increase in the QOL scores was observed at the end of the first month of treatment in both groups. However, these changes were more remarkable in the *jujube* group, which was more significant in physical dimensions. It seems that the lack of liver complications and the induced problems, as well as the significant improvement of cough and constipation in the *jujube* group, have led to the improvement of the physical dimension of QOL.

4.1 | Advantage

Regarding the strengths of the study, one can refer to the novelty, existence of a control group, and provision of a new method to prevent the drug-induced liver enzyme disorders in TB patients. The multicenter nature of this study meant that none of our patients were out of the same center at the same time and did not visit each other. This results in the randomization and blending without the slightest problem. Another advantage of this study was the administration of the drug in the syrup form, which was well received by the patients since it was not the same as all TB drugs that are in tablets. The advantages of the syrup (Oral liquid dosage forms) include ease of swallowing in patients with dysphagia and elderly people; moreover, the dosage can be adjusted easily.[29]

4.2 | Study limitations

The limitation of this study was the small sample size of subjects in both groups. We were unable to recruit tuberculosis patients to the expected number from sample size calculation due to coronavirus epidemic and safety reasons. Accordingly, the research procedure had to be terminated, and the study was conducted as a pilot.

5 | CONCLUSION

According to the results of this study, 10 cc of *jujube* syrup per day for four weeks can play a preventive role against hepatotoxicity caused by anti-TB drugs without any significant side effects. It seems that the presence of phenols and the antioxidant properties of *jujube* can be one of the main mechanisms of liver protection. It can also be useful in controlling the cough in TB patients and improving their QOL. However, a study with larger sample size is required to confirm the results of this study.

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AUTHORS CONTRIBUTIONS

All authors have made significant contributions to formation of concept, design of the study, the collection, analysis and interpretation of data, final conclusion, writing of the manuscript and the response to the reviewer's comments. All authors have seen and approved the final version of the article. And they all agreed to be accountable to all aspects of the work.

DISCLOSURE

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data are not publicly available due to privacy, legal, and ethical restrictions.

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